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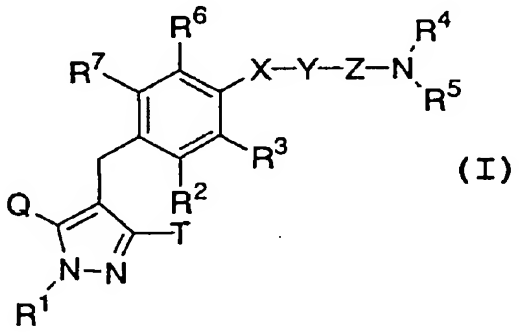
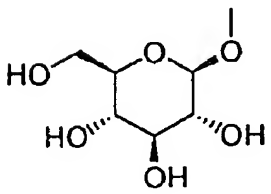
(54) Titre : DERIVE DE PYRAZOLE, COMPOSITION MEDICINALE CONTENANT CE DERIVE, UTILISATION THERAPEUTIQUE DE CEUX-CI ET INTERMEDIAIRE POUR LA PRODUCTION DE CETTE COMPOSITION

(54) Title: PYRAZOLE DERIVATIVE, MEDICINAL COMPOSITION CONTAINING THE SAME, MEDICINAL USE THEREOF, AND INTERMEDIATE FOR PRODUCTION THEREOF



(I)



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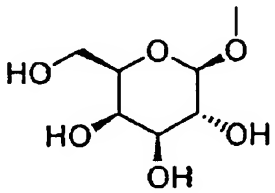
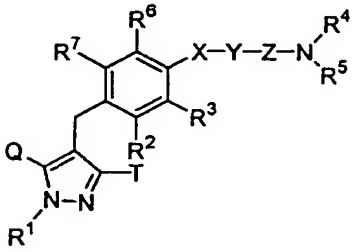


(III)

(57) Abrégé/Abstract:
A pyrazole derivative represented by the general formula (I) (wherein R^1 is H, optionally substituted C_{1-6} alkyl, etc.; either of Q and T is the group of the formula (II) or the formula (III) and the other is optionally substituted C_{1-6} alkyl, etc.; R^2 is H, halogeno, OH, optionally substituted C_{1-6} alkyl, etc.; X is a single bond, O, or S; Y is a single bond, C_{1-6} alkylene, etc.; Z is CO or SO_2; R^4 and R^5 each is H, optionally substituted C_{1-6} alkyl, etc.; and R^3, R^6, and R^7 each is H, halogeno, etc.), a pharmacologically acceptable salt of the derivative, or a prodrug of either. They have excellent human SGLT1 inhibitory activity and are useful as a preventive or therapeutic agent for diseases attributable to hyperglycemia such as diabetes, complications of diabetes, and obesity.

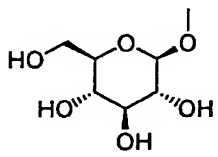
ABSTRACT

The present invention provides pyrazole derivatives represented by the general formula:

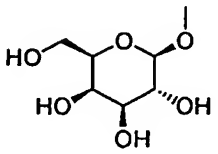


(I)

wherein R^1 represents H, an optionally substituted C_{1-6} alkyl group etc.; one of Q and T represents a group represented by the general formula:



or a group represented by the general formula:

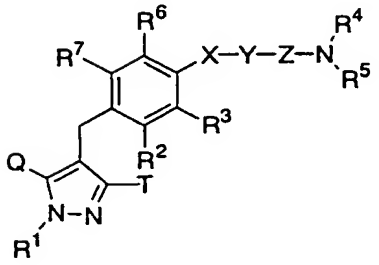


while the other represents an optionally substituted C_{1-6} alkyl group etc.; R^2 represents H, a halogen atom, OH, an optionally substituted C_{1-6} alkyl group etc.; X represents a single bond, O or S; Y represents a single bond, a C_{1-6} alkylene group etc.; Z represents CO or SO_2; R^4 and R^5 represent H, an optionally substituted C_{1-6} alkyl group etc.; and R^3, R^6 and R^7 represent

H, a halogen atom etc., pharmaceutically acceptable salts thereof or prodrugs thereof, which exhibit an excellent inhibitory activity in human SGLT1 and are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications or obesity, and pharmaceutical compositions comprising the same, pharmaceutical uses thereof, and intermediates for production thereof.

CLAIMS

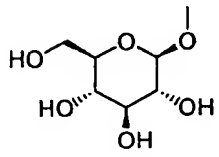
1. A pyrazole derivative represented by the general formula:



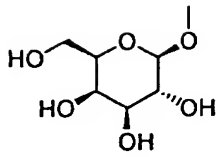
wherein

R^1 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a hydroxy(C_{2-6} alkyl) group, a C_{3-7} cycloalkyl group, a C_{3-7} cycloalkyl-substituted (C_{1-6} alkyl) group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, or an aryl(C_{1-6} alkyl) group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group on the ring;

one of Q and T represents a group represented by the formula:



or a group represented by the formula:



while the other represents a C_{1-6} alkyl group, a halo(C_{1-6} alkyl) group, a C_{1-6} alkoxy-substituted (C_{1-6} alkyl) group or a C_{3-7} cycloalkyl group;

R^2 represents a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a halo(C_{1-6} alkyl) group, a halo(C_{1-6} alkoxy) group, a C_{1-6} alkoxy-substituted (C_{1-6} alkoxy) group, a C_{3-7} cycloalkyl-substituted (C_{2-6} alkoxy) group or a group of the general formula: -A-R^8 in which A represents a single bond, an oxygen atom, a methylene group, an ethylene group, -OCH_2- or -CH_2O-; and R^8 represents a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, a halo(C_{1-6} alkyl) group, a hydroxy(C_{1-6} alkyl) group, a carboxy group, a C_{2-7} alkoxycarbonyl group, a cyano group and a nitro group, or a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group;

X represents a single bond, an oxygen atom or a sulfur atom;

Y represents a single bond, a C_{1-6} alkylene group or a C_{2-6} alkenylene group with the proviso that X is a single bond when Y is a single bond;

Z represents a carbonyl group or a sulfonyl group;

R^4 and R^5 are the same or different, and each represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (i), or they bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group;

R^3, R^6 and R^7 are the same or different, and each represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group; and

substituent group (i) consists of a hydroxy group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a sulfamide group, a mono or di(C_{1-6} alkyl)ureido group, a mono or di(C_{1-6} alkyl)sulfamide group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group, a group of the general formula: $-CON(R^9)R^{10}$ in which R^9 and R^{10} are the same or different, and each represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 substituents selected from the group consisting of a hydroxy group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a mono or di(C_{1-6} alkyl)ureido group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group and a carbamoyl group, or they bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group

consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group, a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, and a C_{1-4} aromatic cyclic amino group which may have a C_{1-6} alkyl group as a substituent,
or a pharmaceutically acceptable salt thereof.

2. A pyrazole derivative as claimed in claim 1, wherein Y represents a C_{1-6} alkylene group or a C_{2-6} alkenylene group; one of R^4 and R^5 represents a C_{1-6} alkyl group which has the same or different 1 to 3 groups selected from the following substituent group (i), the other represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (i); and substituent group (i) consists of a hydroxy group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a sulfamide group, a mono or di(C_{1-6} alkyl)ureido group, a mono or di(C_{1-6} alkyl)sulfamide group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group, a group of the general formula: $-CON(R^9)R^{10}$ in which R^9 and R^{10} are the same or different, and each represents a hydrogen atom

or a C_{1-6} alkyl group which may have the same or different 1 to 3 substituents selected from the group consisting of a hydroxy group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a mono or di(C_{1-6} alkyl)ureido group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group and a carbamoyl group, or they bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group, a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, and a C_{1-4} aromatic cyclic amino group which may have a C_{1-6} alkyl group as a substituent, or a pharmaceutically acceptable salt thereof.

3. A pyrazole derivative as claimed in claim 2, wherein one of R^4 and R^5 represents a C_{1-6} alkyl group which has a group selected from the following substituent group (iA), the other represents a hydrogen atom; and substituent group (iA) is a group of the general formula: $-CON(R^{9A})R^{10A}$ in which R^{9A} and R^{10A} bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic

amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, or a pharmaceutically acceptable salt thereof.

4. A pyrazole derivative as claimed in any one of claims 1-3, wherein X represents a single bond; and Y represents a trimethylene group or a 1-propenylene group, or a pharmaceutically acceptable salt thereof.

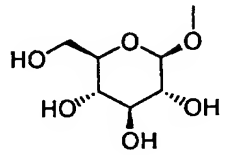
5. A pyrazole derivative as claimed in any one of claims 1-3, wherein X represents an oxygen atom; and Y represents an ethylene group or a trimethylene group, or a pharmaceutically acceptable salt thereof.

6. A pyrazole derivative as claimed in claim 1, wherein X represents a single bond; Y represents a single bond; one of R^4 and R^5 represents a C_{1-6} alkyl group which has the same or different 1 to 3 groups selected from the following substituent group (iB), the other represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (iB); and substituent group (iB) consists of an ureido group, a sulfamide group, a mono or di(C_{1-6} alkyl)ureido group, a mono or di(C_{1-6} alkyl)sulfamide group, a C_{1-6} alkylsulfonylamino group, a group of the general formula: $-CON(R^{9B})R^{10B}$ in which one of R^{9B} and R^{10B} represents a C_{1-6} alkyl group which has the same or different 1 to 3 substituents selected from the group consisting of a hydroxy

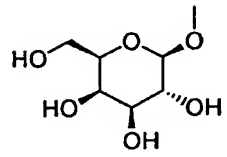
group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a mono or di(C_{1-6} alkyl)ureido group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group and a carbamoyl group, the other represents a hydrogen atom, a C_{1-6} alkyl group which may have the same or different 1 to 3 substituents selected from the group consisting of a hydroxy group, an amino group, a mono or di(C_{1-6} alkyl)amino group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group, an ureido group, a mono or di(C_{1-6} alkyl)ureido group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group and a carbamoyl group, or they bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an amino group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group, a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group, and a C_{1-4} aromatic cyclic amino group which may have a C_{1-6} alkyl group as a substituent, or a pharmaceutically acceptable salt thereof.

7. A pyrazole derivative as claimed in any one of claims 1-6,

wherein R^1 represents a hydrogen atom or a hydroxy(C_{2-6} alkyl) group; T represents a group represented by the formula:

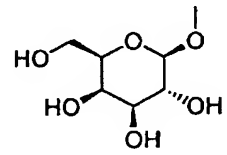


or a group represented by the formula:



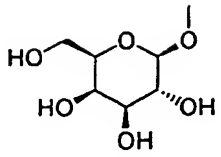
Q represents a C_{1-6} alkyl group or a halo(C_{1-6} alkyl) group; and R^3, R^6 and R^7 represent a hydrogen atom, or a pharmaceutically acceptable salt thereof.

8. A pyrazole derivative as claimed in any one of claims 1-6, wherein one of Q and T represents a group represented by the formula:



the other represents a C_{1-6} alkyl group, a halo(C_{1-6} alkyl) group, a C_{1-6} alkoxy-substituted (C_{1-6} alkyl) group or a C_{3-7} cycloalkyl group, or a pharmaceutically acceptable salt thereof.

9. A pyrazole derivative as claimed in claim 7 or 8, wherein T represents a group represented by the formula:

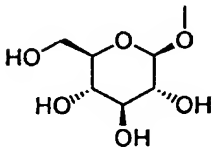


or a pharmaceutically acceptable salt thereof.

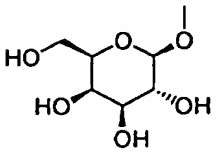
10. A pyrazole derivative as claimed in claim 7 or 9, wherein Q represents an isopropyl group, or a pharmaceutically acceptable salt thereof.

11. A prodrug of a pyrazole derivative as claimed in any one of claims 1-10 or a pharmaceutically acceptable salt thereof.

12. A prodrug as claimed in claim 11, wherein T represents a group represented by the formula:



or a group represented by the formula:



in which the hydroxy group at the 4-position is substituted by a glucopyranosyl group or a galactopyranosyl group, or the hydroxy group at the 6-position is substituted by a glucopyranosyl group, a galactopyranosyl group, a C_{2-7} acyl group,

a C_{1-6} alkoxy-substituted (C_{2-7} acyl) group, a C_{2-7} alkoxycarbonyl-substituted (C_{2-7} acyl) group, a C_{2-7} alkoxycarbonyl group, an aryl(C_{2-7} alkoxycarbonyl) group or a C_{1-6} alkoxy-substituted (C_{2-7} alkoxycarbonyl) group.

13. A pyrazole derivative as claimed in claim 1, which is a compound selected from the following group:

4-[(4-{3-[1-carbamoyl-1-(methyl)ethylcarbamoyl]propyl}-2-methylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-4-[(4-{3-[1-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]propyl}phenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[2-(dimethylamino)ethylcarbamoyl]-1-(methyl)ethylcarbamoyl}propyl)phenyl]methyl}-1*H*-pyrazole;

4-[(4-{3-[1-(2-aminoethylcarbamoyl)-1-(methyl)ethylcarbamoyl]propyl}phenyl)methyl]-3-(β-D-galactopyranosyloxy)-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{3-[1-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]propyl}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-

propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(4-isopropylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{3-[(*S*)-2-hydroxy-1-(methyl)ethylcarbamoyl]propyl}phenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{(1*E*)-3-[(*S*)-2-hydroxy-1-(methyl)ethylcarbamoyl]prop-1-enyl}phenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(2-{1-[(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-ethoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{2-[2-hydroxy-1,1-di-(methyl)ethylcarbamoyl]ethoxy}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{2-[1-{[4-(2-hydroxyethyl)-piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]ethoxy}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(2-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-ethoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propyl)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-

propoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{3-[1-{[4-(2-hydroxyethyl)-piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]propoxy}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}propoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-1-(3-hydroxypropyl)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

4-{[2-fluoro-4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)-ethylcarbamoyl}propyl)phenyl]methyl}-3-(β-D-galacto-pyranosyloxy)-5-isopropyl-1*H*-pyrazole;

4-{[2-chloro-4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)-ethylcarbamoyl}propyl)phenyl]methyl}-3-(β-D-glucopyranosyl-oxy)-5-isopropyl-1*H*-pyrazole, and

pharmaceutically acceptable salts thereof.

14. A pyrazole derivative as claimed in claim 13, which is a compound selected from the following group:

3-(β-D-galactopyranosyloxy)-4-[(4-{3-[1-{[4-(2-hydroxy-ethyl)piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]-propyl}phenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-

[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{3-[1-{[4-(2-hydroxyethyl)-piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]-propyl}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propyl)phenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(2-{1-[(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-ethoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-4-[(4-{2-[1-{[4-(2-hydroxyethyl)-piperazin-1-yl]carbonyl}-1-(methyl)ethylcarbamoyl]ethoxy}-2-methylphenyl)methyl]-5-isopropyl-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(2-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-ethoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propyl)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-glucopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

3-(β-D-galactopyranosyloxy)-5-isopropyl-4-{[4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)ethylcarbamoyl}-propoxy)-2-methylphenyl]methyl}-1*H*-pyrazole;

4-{[2-fluoro-4-(3-{1-[(piperazin-1-yl)carbonyl]-1-(methyl)-

ethylcarbamoyl}propyl)phenyl]methyl}-3-(β-D-galacto-pyranosyloxy)-5-isopropyl-1*H*-pyrazole, and pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition comprising as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

16. A human SGLT1 inhibitor comprising as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

17. An agent for inhibiting postprandial hyperglycemia comprising as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

18. An agent for the prevention or treatment of a disease associated with hyperglycemia, which comprises as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

19. An agent for the prevention or treatment as claimed in claim 18, wherein the disease associated with hyperglycemia is a disease selected from the group consisting of diabetes,

impaired glucose tolerance, diabetic complications, obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia and gout.

20. An agent for the inhibition of advancing impaired glucose tolerance or impaired fasting glycemia into diabetes in a subject, which comprises as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

21. An agent for the prevention or treatment of a disease associated with the increase of blood galactose level, which comprises as an active ingredient a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

22. An agent for the prevention or treatment as claimed in claim 21, wherein the disease associated with the increase of blood galactose level is galactosemia.

23. A pharmaceutical composition as claimed in claim 15, wherein the dosage form is sustained release formuation.

24. An agent as claimed in any one of claims 16-22, wherein the dosage form is sustained release formuation.

25. A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

26. A method for the inhibition of advancing impaired glucose tolerance into diabetes in a subject, which comprises administering an effective amount of a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof.

27. A use of a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

28. A use of a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a pharmaceutical composition for the inhibition of advancing impaired glucose tolerance into diabetes in a subject.

29. A pharmaceutical combination which comprises (A) a pyrazole derivative as claimed in any one of claims 1-14, a

pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor,

probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

30. A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase

stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a

bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

31. A method for the inhibition of advancing impaired glucose tolerance into diabetes in a subject, which comprises administering an effective amount of (A) a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol,

a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin

receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

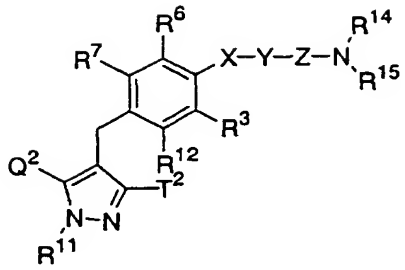
32. A use of (A) a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-

dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

33. A use of (A) a pyrazole derivative as claimed in any one of claims 1-14, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase

inhibitor, a fibric acid derivative, a β_3-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer, for the manufacture of a pharmaceutical composition for the inhibition of advancing impaired glucose tolerance into diabetes in a subject.

34. A pyrazole derivative represented by the general formula:



wherein

R^{11} represents a hydrogen atom, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a hydroxy(C_{2-6} alkyl) group which may have a protective group, a C_{3-7} cycloalkyl group, a C_{3-7} cycloalkyl-substituted (C_{1-6} alkyl) group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group which may have a protective group, an amino group which may have a protective group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, or an aryl(C_{1-6} alkyl) group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group which may have a protective group, an amino group which may have a protective group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group on the ring;

one of Q^2 and T^2 represents a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy group or a 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy group, while the other represents a C_{1-6} alkyl group, a halo(C_{1-6} alkyl) group, a C_{1-6} alkoxy-substituted (C_{1-6} alkyl) group or a C_{3-7} cycloalkyl group;

R^{12} represents a hydrogen atom, a halogen atom, a hydroxy group which may have a protective group, a C_{1-6} alkyl group,

a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a halo(C_{1-6} alkyl) group, a halo(C_{1-6} alkoxy) group, a C_{1-6} alkoxy-substituted (C_{1-6} alkoxy) group, a C_{3-7} cycloalkyl- substituted (C_{2-6} alkoxy) group or a group of the general formula: -A-R^{18} in which A represents a single bond, an oxygen atom, a methylene group, an ethylene group, $-OCH_2-$ or $-CH_2O-$; and R^{18} represents a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group which may have a protective group, an amino group which may have a protective group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, a halo(C_{1-6} alkyl) group, a hydroxy(C_{1-6} alkyl) group which may have a protective group, a carboxy group which may have a protective group, a C_{2-7} alkoxycarbonyl group, a cyano group and a nitro group, or a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group;

X represents a single bond, an oxygen atom or a sulfur atom;

Y represents a single bond, a C_{1-6} alkylene group or a C_{2-6} alkenylene group with the proviso that X is a single bond when Y is a single bond;

Z represents a carbonyl group or a sulfonyl group;

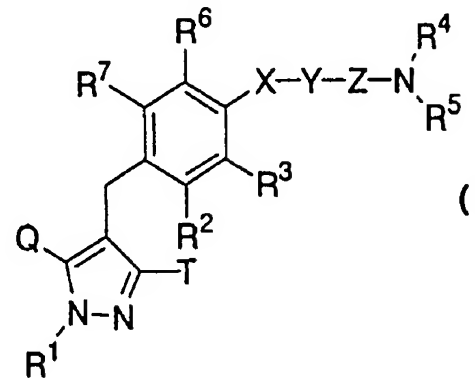
R^{14} and R^{15} are the same or different, and each represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 groups selected from the following substituent group (ii), or they bind together with the neighboring nitrogen

atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group which may have a protective group;

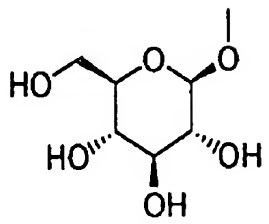
R^3, R^6 and R^7 are the same or different, and each represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group; and

substituent group (ii) consists of a hydroxy group which may have a protective group, an amino group which may have a protective group, a mono or di(C_{1-6} alkyl)amino group which may have a protective group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group which may have a protective group, an ureido group, a sulfamide group, a mono or di(C_{1-6} alkyl)ureido group, a mono or di(C_{1-6} alkyl)sulfamide group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group, a group of the general formula: $-CON(R^{19})R^{20}$ in which R^{19} and R^{20} are the same or different, and each represents a hydrogen atom or a C_{1-6} alkyl group which may have the same or different 1 to 3 substituents selected from the group consisting of a hydroxy group which may have a protective group, an amino group which may have a protective group, a mono or di(C_{1-6} alkyl)amino group which may have a protective group, a mono or di[hydroxy(C_{1-6} alkyl)]amino group which may have a protective group, an ureido group, a mono or di(C_{1-6} alkyl)ureido group, a C_{2-7} acylamino group, a C_{1-6} alkylsulfonylamino group and a carbamoyl group, or they bind together with the neighboring nitrogen atom to form a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group which may have a protective

group, a C_{3-7} cycloalkyl group, a C_{2-6} heterocycloalkyl group, an aryl group which may have the same or different 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group which may have a protective group, an amino group which may have a protective group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, a heteroaryl group which may have a substituent selected from the group consisting of a halogen atom and a C_{1-6} alkyl group, a C_{2-6} cyclic amino group which may have a substituent selected from the group consisting of a C_{1-6} alkyl group and a hydroxy(C_{1-6} alkyl) group which may have a protective group, and a C_{1-4} aromatic cyclic amino group which may have a C_{1-6} alkyl group as a substituent, or a salt thereof.



(I)



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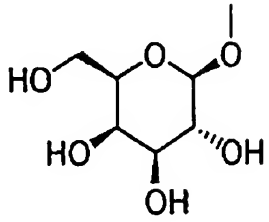

(III)